PSJ2 Exh 19

NUCYNTA® ER Frequently Asked Questions (FAQs)

You may encounter the following questions when discussing NUCYNTA® ER with customers. These questions relate to the information you are presenting on your iPad and to NUCYNTA® ER in general.

Do not discuss, show, or leave behind these FAQs with customers. If you receive unsolicited questions from a customer regarding this information, please have the customer sign and submit an electronic Medical Information Request, or fax in a hard copy of the Medical Information Request form. Be sure to include the following information in the request:

- Requester name and contact information
- Date of request
- Specific verbatim question
- Method in which requester wants response
- Signature of HCP initiating request
- Name of company employee who interacted with HCP

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Table of Contents

Efficacy

"Are there additional studies for NUCYNTA® ER?"

- Doctor, I'm excited that you're interested in NUCYNTA® ER and its great clinical profile. We are going to review this information with you in the future. For the launch of NUCYNTA® ER, we are focused on our chronic low back pain study, one of the most prevalent conditions you see in your practice.
- With that, my goal is to help make you confident that NUCYNTA® ER provides powerful pain management for your patients with moderate to severe chronic pain[1,2]. [Buynak, p3, col 1, ¶2; p5, col 2, ¶3] [Schwartz, p156, col 2, Fig 2; p160, col 1, ¶3]
- I encourage you to register for our Web-based, peer-to-peer educational programs, where you can review and discuss clinical data for NUCYNTA® ER with noted thought leaders.
- Would you like me to help you register?

"I heard about the 1-year safety study and diabetic peripheral neuropathy study at a speaker program."

- Doctor, I'm excited that you're interested in NUCYNTA® ER and its great clinical profile. If you would like more information, I am happy to have those studies sent to you.
- We are going to review this information with you in the future. For the launch of NUCYNTA® ER, we are focused on our chronic low back pain study, one of the most prevalent conditions you see in your practice.
- With that, my goal is to help make you confident that NUCYNTA® ER provides powerful pain management for your patients with moderate to severe chronic pain[1,2]. [Buynak, p3, col 1, ¶2; p5, col 2, ¶3] [Schwartz, p156, col 2, Fig 2; p160, col 1, ¶3]
- (Use the iPad Assets to redirect to Chronic Low Back Pain to ensure your customers are sold on the efficacy of NUCYNTA® ER)

"How long until the patient will first feel pain relief on NUCYNTA® ER?"

- NUCYNTA® ER was not designed to produce rapid onset for the treatment of acute pain, rather it is designed to manage chronic pain over an extended period of time.
- For this reason, the clinical trials did not specifically measure onset of action because it is an extended-release formulation. The Phase III clinical trials of NUCYNTA® ER measured pain intensity based on a 0-10 numerical rating scale (0=no pain and 10=pain as bad as you can imagine). Pain was measured twice daily by patients in pain diaries[1,2]. [Citations: Buynak et al, p.1789, col2, Schwartz et al,p153, col1]
- If you have further questions about this trial design, I can submit a Medical Information Request for you.

Tolerability Profile

"Why are the discontinuation rates so high with oxycodone CR? I don't see that in my practice."

- I understand how this figure might be different from what you've seen in your practice
- Discontinuation rates in a practice setting may differ from those in a randomized, clinical trial
- In this trial, the high discontinuation rates were due in part to the high incidence of adverse events with oxycodone CR[1] [Buynak, p1791, col 1, ¶3]
- In fact, 62% of patients in the oxycodone group experienced GI adverse events and 44% of patients in the NUCYNTA® ER group experienced GI adverse events[1] [Buynak, p1798, Table 3]
- In the NUCYNTA® ER and oxycodone CR groups, 16.7% and 31.7% of patients, respectively, reported treatment-emergent adverse events that led to study discontinuation[1] [Buynak, p1797, col 1, ¶2]
- Doctor, would you agree that discontinuation rates are an important consideration? Do you see how the favorable tolerability profile of NUCYNTA® ER could benefit your chronic pain patients?

Mechanism of Action

"How does NUCYNTA® ER work to relieve pain?"

- Tapentadol is a centrally-acting synthetic analgesic; the exact mechanism of action is unknown.
- Although the clinical relevance is unclear, preclinical animal studies have shown that tapentadol is a mu-opioid agonist, as well as a norepinephrine reuptake inhibitor.

"How much does norepinephrine reuptake inhibition contribute to analgesia vs mu-opioid agonism?"

- That's an interesting question, Doctor
- However, we currently don't have data that identify the specific effects of each mechanism
- Although the clinical relevance is unclear, preclinical animal studies have shown that tapentadol is a mu-opioid agonist and a norepinephrine reuptake inhibitor
- In contrast, traditional opioids primarily target mu-opioid receptors[3,4] [Vanderah, p 2,¶5; p3,¶1&4; p4, ¶3-4; p5, ¶1] [Rosenblum, p4, ¶2]

"Does norepinephrine work more quickly in chronic pain vs depression?"

- Doctor, while I would like to be able to provide you with an answer, we have no data to address this question at this time

- It is important to keep in mind, however, that the role of norepinephrine in chronic pain vs depression should not be compared as these are different and separate conditions.

"Which subunit of the mu-opioid receptor does NUCYNTA® ER bind to?"

- Doctor, while I realize you would be interested in finding out this information, the binding and effects of tapentadol on mu-opioid receptor subtypes have not been evaluated
- There is very little evidence that mu-opioid receptor-selectivity (or nonselectivity) has any functional consequence for a mu-opioid receptor agonist

"Does NUCYNTA® ER inhibit serotonin reuptake?"

- As stated in the full Prescribing Information, Doctor, tapentadol is a centrally-acting analgesic
- However, the exact mechanism of action is unknown
- Although the clinical relevance is unclear, preclinical animal studies have shown that tapentadol is a mu-opioid agonist and a norepinephrine reuptake inhibitor.

Tolerance and Withdrawal Symptoms

"Can patients develop tolerance to NUCYNTA® ER?"

- Yes, Doctor, as with all opioids, tolerance can develop with NUCYNTA® ER
- Please see Section 9.3 of the full Prescribing Information titled *Dependence* for further information

"In the withdrawal analysis for NUCYNTA® ER, how long were patients on therapy before they discontinued?"

- Doctor, I can understand why you would want to know this, given the chronic nature of your patients' pain conditions
- The opioid withdrawal data are from Phase II and Phase III studies, including one safety study that lasted up to 1 year.
- In these studies, patients taking NUCYNTA® ER who stopped abruptly without initiating alternative opioid therapy were assessed for withdrawal symptoms 2 to 4 days after discontinuation using the Clinical Opiate Withdrawal Scale (COWS).[5]
- As with other opioid analgesics, withdrawal symptoms may be reduced by tapering NUCYNTA® ER.
- [Ref 5: DOF, Integrated Summary of Safety, Section 5.6.2.1]
- Doctor, do you see how the favorable tolerability profile of NUCYNTA® ER could benefit your chronic pain patients?

Tolerance and Withdrawal Symptoms (cont)

"How was this withdrawal analysis conducted?"

- Doctor, I can understand why you would want to know this, given the chronic nature of your patients' pain conditions
- The pie chart includes opioid withdrawal data from Phase II and Phase III studies, including a safety study that lasted up to 1 year
- In these studies, patients taking NUCYNTA® ER who stopped abruptly without initiating alternative opioid therapy were assessed for withdrawal symptoms between 2 to 4 days after discontinuation, using the Clinical Opiate Withdrawal Scale (COWS)[5] [DOF, Integrated Summary of Safety, Section 5.6.2.1]
- There were 635 patients in the NUCYNTA® ER group assessed between Day 2 and Day 4 after abrupt cessation of treatment, with 12% and 2% of patients having mild or moderate withdrawal, respectively[5] [DOF, Integrated Summary of Safety, Section 5.6.2.1]

Dosing, Titration, and Conversion

"Why is 500 mg of NUCYNTA® ER the highest daily dose?"

- Total daily doses greater than 500 mg of NUCYNTA® ER have not been studied, and therefore, a dose of 500 mg should not be exceeded.
- The recommended NUCYNTA® ER maintenance dose is 100 mg to 250 mg twice daily.
- Individually titrate the dose within the therapeutic range of 100 mg to 250 mg twice daily.

"Are there equianalgesic dose conversions from other mu-opioid agonists to NUCYNTA® ER?"

- There are no adequate data on the direct conversion from other opioids to NUCYNTA® ER.
- The initial dose of NUCYNTA® ER in patients previously taking other opioids is 50 mg, titrated to an effective and tolerable dose within the therapeutic range of 100 mg to 250 mg twice daily.
- Although there are no data on conversion from other opioids to NUCYNTA® ER, the pivotal trial for chronic low back pain was designed with a dose ratio of 5:1 for NUCYNTA® ER to oxycodone CR.
- Therefore, 20 mg to 50 mg of oxycodone CR and 100 mg to 250 mg of NUCYNTA® ER were studied.
- The trial was not designed to establish equianalgesic doses.
- Treatment should be individualized for the patient, and clinical judgment should be used to guide dosing and titration.

Dosing, Titration, and Conversion (cont)

"How do I convert from other opioids to NUCYNTA® ER?

- Doctor, while I would like to provide you with that information, there are no adequate data on the direct conversion from other opioids to NUCYNTA® ER
- The initial dose of NUCYNTA® ER in patients previously taking other opioids is 50 mg, titrated to an effective and tolerable dose within the therapeutic range of 100 mg to 250 mg twice daily. This 50-mg twice-daily dose is only a starting point, close observation and titration are indicated until a satisfactory dose is obtained on the new therapy.
- Although there are no data on conversion from other opioids to NUCYNTA® ER, the pivotal trial for chronic low back pain was designed with a dose ratio of 5:1 for NUCYNTA® ER to oxycodone CR. Therefore, 20 mg to 50 mg of oxycodone CR and 100 mg to 250 mg of NUCYNTA® ER were studied
- The trial was not designed to establish equianalgesic doses
- Treatment should be individualized for the patient and clinical judgment should be used to guide dosing and titration
- I can leave a reprint of the published study with you for your review
- If you have further questions about this, I can submit a Medical Information Request for you

"How do I convert patients from NUCYNTA® to NUCYNTA® ER?"

- Patients can be converted from NUCYNTA® to NUCYNTA® ER using the equivalent total daily dose of NUCYNTA® and dividing it into 2 equal doses of NUCYNTA® ER, separated by approximately 12-hour intervals.
- As an example, a patient receiving 50 mg of NUCYNTA® 4 times per day (200 mg/day) may be converted to 100 mg NUCYNTA® ER twice a day.
- This was demonstrated in a clinical study in which patients with moderate to severe low back pain receiving NUCYNTA® immediate-release tablets every 4 to 6 hours were switched to an equivalent total daily dose of NUCYNTA® ER (extended-release) tablets, with NUCYNTA® ER providing equivalent efficacy and similar tolerability.[7]
- [Ref 7: Etropolski, p63, Fig 1; col 2, ¶1-2; p67, col 1, ¶1; Fig 3; p69, Table 2]

Dosing, Titration, and Conversion (cont)

"Is the starting dose the same for opioid-experienced vs opioid-naïve patients?"

- Yes, the initial dose of NUCYNTA® ER for both opioid-naïve patients and patients previously taking other opioids is 50 mg twice a day (approximately every 12 hours)
- Individually titrate the dose within the therapeutic range of 100 mg to 250 mg twice daily
- Keep in mind, there are no adequate data on the direct conversion from other opioids to NUCYNTA® ER
- Please note, however, that you may start with a dose greater than 50 mg twice daily in patients already receiving NUCYNTA®
- Patients can be converted from NUCYNTA® to NUCYNTA® ER using the equivalent total daily dose of NUCYNTA® and dividing it into 2 equal doses, separated by approximately 12-hour intervals
- Let me provide you with the NUCYNTA® ER Titration and Dose Conversion Guide for your reference

"What is the ceiling dose of NUCYNTA® ER?"

- Doctor, there is no established ceiling dose for NUCYNTA® ER
- As you know, a ceiling dose is the threshold at which additional dose increases do not lead to greater efficacy
- We don't know whether this plateau effect occurs with NUCYNTA® ER, because total daily doses greater than 500 mg have not been studied
- Therefore, as stated in the approved Prescribing Information, do not exceed a total daily dose of NUCYNTA® ER of 500 mg
- Please note that the recommended NUCYNTA® ER maintenance dose is 100 mg to 250 mg twice daily
- Individually titrate the dose within the therapeutic range of 100 mg to 250 mg twice daily

Note to Sales Representatives: A ceiling dose is the threshold at which additional dose increases produce no change in efficacy and often lead to greater side effects. It is a plateau effect that is common to most medications. However, it is important to note that pure opioid agonists, such as morphine, do not have a ceiling dose.

Dosing, Titration, and Conversion (cont)

"How do I titrate a patient?"

- In your practice you may titrate your patients at your discretion, based on your assessment of their pain management needs.
- The starting dose of NUCYNTA® ER is 50 mg twice daily, titrated to an effective and tolerable dose within the therapeutic range of 100 mg to 250 mg twice daily.
- The 50-mg, twice-daily dose is only a starting point, and close observation and titration are indicated until a satisfactory dose is obtained on the new therapy.
- After starting with 50 mg of NUCYNTA® ER, titrate patients to adequate analgesia with dose increases of 50 mg no more than twice daily, every 3 days.
- Visit www.nucynta.com to view and/or download the NUCYNTA® ER Titration and Dose Conversion Guide.
- Individually titrate the dose to the patients needs.

"How quickly can I increase the dose of NUCYNTA® ER?"

- After starting with NUCYNTA® ER 50 mg, titrate patients to adequate analgesia with dose increases of 50 mg no more than twice daily, every 3 days
- In clinical studies, patients received the following titration regimen for NUCYNTA® ER
    - Patients started therapy on 50 mg twice daily
    - After 3 days, patients were titrated up to 100 mg twice daily
    - After another 3 days, patients were allowed to be titrated, at 3-day intervals, to an optimal dose (maximum of 250 mg twice daily) over the following 3 weeks
- Let me provide you with the NUCYNTA® ER Titration and Dose Conversion Guide for your reference

Dosing, Titration, and Conversion (cont)

"Why was the 50-mg dose not studied for efficacy?"

- This is an important topic, Doctor, which I'm happy to discuss with you
- Please note that the 50-mg dose is used for titration and to initiate therapy in patients not currently receiving NUCYNTA®
- Remember, 50 mg twice daily is *not a maintenance dose*
- The 50-mg twice-daily dose is only a starting point, and close observation and titration are indicated until a satisfactory dose is obtained on the new therapy
- The recommended maintenance dose of NUCYNTA® ER is 100 mg to 250 mg twice daily
- This is equivalent to a total daily dose of 200 mg to 500 mg
- In patients who were not previously receiving NUCYNTA®, after starting with 50 mg twice daily, titrate to an effective and tolerable dose within the therapeutic range of 100 mg to 250 mg twice daily
- Doctor, have I explained clearly that the 50-mg twice daily dose is not a maintenance dose?

"What is the maximum dose for patients if I use both NUCYNTA® and NUCYNTA® ER together?"

- Doctor, the Prescribing Information states that you should discontinue all other tapentadol and tramadol products in patients who are starting or currently receiving NUCYNTA® ER
- Patients should not take NUCYNTA® and NUCYNTA® ER simultaneously
- However, I can discuss the maximum recommended total daily doses of NUCYNTA® and NUCYNTA® ER *individually*
- The maximum recommended total daily dose of NUCYNTA® ER is 500 mg
- The maximum recommended total daily dose of NUCYNTA® is 700 mg on the first day of therapy and 600 mg on subsequent days
- Should you wish to transition a patient from NUCYNTA® to NUCYNTA® ER, you can do so as follows:
- Patients can be converted from NUCYNTA® to NUCYNTA® ER using the equivalent total daily dose of NUCYNTA® and dividing it into 2 equal doses, separated by approximately 12-hour intervals

Dosing, Titration, and Conversion (cont)

"What if I switched a patient from oxycodone CR to NUCYNTA® ER, but the patient has requested a switch back to oxycodone CR?"

- What is the reason the patient has requested a switch? Is it due to financial reasons, adverse events, or lack of efficacy?
- If due to adverse events (which includes lack of efficacy or failure of pharmacologic action) for NUCYNTA® ER, this needs to be reported as per company policy
- Were the appropriate dosing and titration guidelines in the full Prescribing Information for NUCYNTA® ER followed in order to maintain adequate efficacy with acceptable tolerability?
- If the patient complains of lack of efficacy because he or she did not experience the same "buzz" or other similar feelings that were associated with oxycodone CR use, then it is important to find out whether the patient did, in fact, receive effective analgesia while taking NUCYNTA® ER
    - This can be done by evaluating the patient's pain intensity or level of pain relief with a valid measurement tool
- Euphoria is a known side effect of opioid use, and the NUCYNTA® ER Prescribing Information describes euphoric mood as an adverse event; it is not a therapeutic endpoint, as the goal of treatment is the management of moderate to severe chronic pain.
- Therefore, it is important for you and the patient to determine whether the therapeutic goals that were established when initiating treatment with NUCYNTA® ER were achieved.

Can I use NUCYNTA® and NUCYNTA® ER together?

- The Prescribing Information states that all other tapentadol and tramadol products should be discontinued in patients who are starting or currently receiving NUCYNTA® ER.
- Patients should not take NUCYNTA® and NUCYNTA® ER simultaneously.

Dosing, Titration, and Conversion (cont)

"What is the maximum dose for patients if I use both NUCYNTA® and NUCYNTA® ER together?"

- Doctor, the Prescribing Information states that you should discontinue all other tapentadol and tramadol products in patients who are starting or currently receiving NUCYNTA® ER
- Patients should not take NUCYNTA® and NUCYNTA® ER simultaneously
- However, I can discuss the maximum recommended total daily doses of NUCYNTA® and NUCYNTA® ER *individually*
- The maximum recommended total daily dose of NUCYNTA® ER is 500 mg
- The maximum recommended total daily dose of NUCYNTA® is 700 mg on the first day of therapy and 600 mg on subsequent days
- Should you wish to transition a patient from NUCYNTA® to NUCYNTA® ER, you can do so as follows:
- Patients can be converted from NUCYNTA® to NUCYNTA® ER using the equivalent total daily dose of NUCYNTA® and dividing it into 2 equal doses, separated by approximately 12-hour intervals

"What if I switched a patient from oxycodone CR to NUCYNTA® ER, but the patient has requested a switch back to oxycodone CR?"

- What is the reason the patient has requested a switch? Is it due to financial reasons, adverse events, or lack of efficacy?
- If due to adverse events (which includes lack of efficacy or failure of pharmacologic action) for NUCYNTA® ER, this needs to be reported as per company policy
- Were the appropriate dosing and titration guidelines in the full Prescribing Information for NUCYNTA® ER followed in order to maintain adequate efficacy with acceptable tolerability?
- If the patient complains of lack of efficacy because he or she did not experience the same "buzz" or other similar feelings that were associated with oxycodone CR use, then it is important to find out whether the patient did, in fact, receive effective analgesia while taking NUCYNTA® ER
    - This can be done by evaluating the patient's pain intensity or level of pain relief with a valid measurement tool
- Euphoria is a known side effect of opioid use, and the NUCYNTA® ER Prescribing Information describes euphoric mood as an adverse event; it is not a therapeutic endpoint, as the goal of treatment is the management of moderate to severe chronic pain
- Therefore, it is important for you and the patient to determine whether the therapeutic goals that were established when initiating treatment with NUCYNTA® ER were achieved

Dosing, Titration, and Conversion (cont)

"What if my patients don't achieve adequate pain relief after starting NUCYNTA® ER?"

- Doctor, please note that the therapeutic range of NUCYNTA® ER is *100 mg to 250 mg twice daily*
- After initiating therapy with NUCYNTA® ER 50 mg twice daily, titrate to an effective and tolerable dose within the therapeutic range of 100 mg to 250 mg twice daily. This 50-mg twice-daily dose is only a starting point, close observation and titration are indicated until a satisfactory dose is obtained on the new therapy
- The maintenance dose range for NUCYNTA® ER is *100 mg to 250 mg twice daily.*
- Keep in mind, total daily doses greater than 500 mg of NUCYNTA® ER have not been studied; therefore, as stated in the approved Prescribing Information, do not exceed a total daily dose of NUCYNTA® ER of 500 mg
- Let me provide you with the NUCYNTA® ER Titration and Dose Conversion Guide for your reference

"What are the dosing recommendations for breakthrough pain?"

- We don't currently have data to address this question
- NUCYNTA® ER is indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
- Let me remind you again that the therapeutic dose range is 100 mg to 250 mg twice daily
- If you would like additional information, I would be happy to submit an electronic Medical Information Request to our Customer Communication Center, and they will follow up with you

Dosing, Titration, and Conversion (cont)

"If a patient has pills remaining and the HCP recommends taking a higher dose, can the patient take multiple pills to get to the desired dosage strength?"

- Doctor, I understand that this is a logistical consideration especially when starting a patient on the 50mg BID dose and then titrating the patient up to a therapeutic dose range of 100-250mg BID.
- From a safety standpoint, taking two 50mg NUCYNTA® ER tablets should produce a similar effect as a single 100mg NUCYNTA® ER tablet. The results of a pharmacokinetic study showed that a dose of two 50mg tablets was slightly less than bioequivalent to a single 100mg dose[5]. [DOF CSR PAI-1063, Results/Conclusions] While the efficacy of taking two 50mg tablets compared to a single 100mg tablet has not been evaluated, a Phase III trial allowed for different tablet strength combinations [5]. [DOF CSR PAI-3027].
  Note to Sales Representatives: this Phase III trial is not yet published.
- At this time, there is only pharmacokinetic data comparing two 50mg tablets vs. a single 100mg tablet. Other dosage strength combinations have not been studied.
- As stated in the package insert, NUCYNTA® ER tablets must be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
- As with many centrally acting analgesic medications, the dosing regimen of NUCYNTA® ER should be individualized according to the severity of pain being treated, the previous experience with similar drugs and the ability to follow-up and provide oversight of treatments.
- If you have further questions about this, I can submit a Medical Information Request for you

"Can NUCYNTA® ER be taken on an empty stomach?"

- Yes, NUCYNTA® ER may be taken with or without food.

Contraindications, Warnings, and Precautions

"Is it safe for patients to consume alcohol while taking NUCYNTA® ER?"

- Use NUCYNTA® ER with caution in patients currently using specified centrally acting drugs or alcohol.
- Patients must not consume alcoholic beverages, or prescription, or nonprescription medications containing alcohol.
- Co-ingestion of alcohol with NUCYNTA® ER may result in a potentially fatal overdose of tapentadol.
- NUCYNTA® ER may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression (CNS), because respiratory depression, hypotension, hypertension, and profound sedation, coma, or death may result.

"What are the contraindications associated with NUCYNTA® ER?"

- Patients with significant respiratory depression, or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment
- Any patient who has or is suspected of having a paralytic ileus
- Patients who are receiving monoamine oxidase (MAOIs) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels, which may result in adverse cardiovascular events
- Patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product. Angioedema has been reported in association with use of tapentadol

Adverse Reactions

What adverse events can occur while taking NUCYNTA® ER?

- NUCYNTA® ER was extensively evaluated in multiple pain models.
- The most common adverse reactions (reported by ≥10% in any NUCYNTA® ER dose group) were nausea, constipation, headache, dizziness, and somnolence.
- For adverse events reported by ≥1% of NUCYNTA® ER-treated patients, please see Table 1 in the Adverse Reactions section in the full Prescribing Information. (Please see the full Prescribing information for complete information on AEs.)

Formulation, Tamper Resistance and Abuse

"What makes NUCYNTA® ER extended-release? Can you tell me more about the NUCYNTA® ER coating technology?"

- Doctor, I appreciate your interest in understanding the extended-release properties of NUCYNTA® ER.
- NUCYNTA® ER tablets are composed of a polymer matrix which allows for tapentadol to slowly diffuse out over time[5]. [Citation: DOF, NDA 3.2.P.2.2 Drug Product, p 9] Due to these extended-release properties, NUCYNTA® ER can be taken approximately every 12 hours. The film-coating does not contribute to its extended-release properties.
- The exact drug release specifications cannot be disclosed as they are proprietary.
- If you have further questions about this, I can submit a Medical Information Request for you.

"Does NUCYNTA® ER stay in the body longer than NUCYNTA® because of its extended-release properties even if the half-life for the NUCYNTA® molecule is 5 hours?"

- Doctor, as you know the half-life is the time required for plasma concentrations to decrease by one-half after absorption and distribution are complete.
- Extended-release technology was developed to compensate for drugs that have a short half-life. Extended-release technology affects an active moiety's absorption pattern not necessarily the elimination rate of the active moiety.
- Therefore, the time to washout for NUCYNTA® ER would be longer than you would see with NUCYNTA®.
- If you have further questions about this, I can submit a Medical Information Request for you.

"Can NUCYNTA® ER tablets be split or crushed?"

- The NUCYNTA® ER formulation was designed to not be amenable to splitting, crushing, or dissolution.
- Like all long-acting opioids, there is no postmarketing experience with NUCYNTA® ER tablets to assess whether the formulation deters abuse, misuse, or diversion.

Formulation, Tamper Resistance and Abuse (cont)

"Is NUCYNTA® ER tamper resistant, and if so, does the tamper-resistant formulation (TRF) reduce abuse potential?"

- The NUCYNTA® ER formulation was designed to not be amenable to crushing or dissolution
- Like all long-acting opioids, there is no postmarketing experience with NUCYNTA® ER tablets to assess whether the formulation deters abuse, misuse, or diversion
- If you would like additional information, I would be happy to submit an electronic Medical Information Request to our Customer Communication Center, and they will follow up with you

"Do you have data on lower abuse potential?"

- Like all long-acting opioids, there is insufficient postmarketing experience with NUCYNTA® ER tablets to assess whether the formulation deters abuse, misuse, or diversion
- Keep in mind, NUCYNTA® ER is a Schedule II controlled substance and can be abused in a manner similar to other opioid agonists
- You should use your medical judgment to determine appropriate patients for NUCYNTA® ER
- If you would like additional information, I would be happy to submit an electronic Medical Information Request to our Customer Communication Center, and they will follow up with you

"Does NUCYNTA® ER have the same tamper-resistant formulation as oxycodone CR?"

- No, the formulation for NUCYNTA® ER is different from the formulation for Oxycodone CR
- If you would like additional information, I would be happy to submit an electronic Medical Information Request to our Customer Communication Center, and they will follow up with you
  Note to Sales Representative: We do not currently have any comparative information between the formulations of NUCYNTA® ER and Oxycodone CR.

Overdose

"How do you reverse an overdose with NUCYNTA® ER?

- Doctor, I can understand your concern about managing a potential overdose with NUCYNTA® ER
- Management of overdose should be focused on treating symptoms of mu-opioid agonism, with primary attention given to reestablishment of a patent airway and institution of assisted or controlled ventilation
- Supportive measures (including oxygen and vasopressors) should be employed in the management of cardiac and/or pulmonary failure as needed
- Cardiac arrest or arrhythmias may require cardiac massage or defibrillation
- Remember to take into account the extended-release characteristics of NUCYNTA® ER when treating overdose
- Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects
- Pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose
    - Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist
    - Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose
    - If the response to the initial administration of opioid antagonists is suboptimal or only brief, repeated doses or an alternative antagonist should be administered as directed by the label of the antagonist
- Only administer opioid antagonists in the presence of clinically significant respiratory or circulatory depression secondary to tapentadol overdose
- In patients who are physically dependent on any opioid agonist, including NUCYNTA® ER, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome
- The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered
- For additional information about overdosage, please see Section 10 of the full Prescribing Information

Use With Other Medications

"Is it safe for a patient to take a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) concomitantly with NUCYNTA® ER?"

- I can certainly understand why you would want to know this information
- There have been postmarketing reports of serotonin syndrome with concomitant use of tapentadol and serotonergic drugs (note that this may occur within the recommended dose).
- Therefore, caution is advised when NUCYNTA® ER is coadministered with other drugs that may affect serotonergic neurotransmitter systems, such as SSRIs, SNRIs, MAOIs, and triptans.
- If concomitant treatment of NUCYNTA® ER with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
- NUCYNTA® ER is contraindicated in patients taking MAOIs within the last 14 days.
- Safety considerations for concurrent use of tapentadol and serotonergic drugs are found in the Warnings and Precautions section (*Section 5*) of the NUCYNTA® ER Prescribing Information.
- Concomitant use of SSRIs, SNRIs, and triptans with NUCYNTA® ER are not contraindicated.

Use With Other Medications (cont)

"What concomitant medications did patients receive in clinical trials of NUCYNTA® ER?"

- In clinical trials with NUCYNTA® ER, SSRIs were permitted for patients with diagnosed psychiatric or neurological conditions, if taken at a stable dose for more than 3 months prior to randomization[5] [DOF, CSR 3011, p39, ¶6] [DOF, CSR 3015, p37, ¶1-2, ¶6] [DOF, CSR 3007, p32, ¶2, ¶4, ¶7]
- Patients should be advised to inform you if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions
- Although specific information about products and doses is not available, the table below lists serotonergic medications permitted and prohibited in clinical trials with NUCYNTA® ER

Study	Prohibited Medications	Permitted Medications
Chronic Low Back Pain [DOF, CSR 3011, p39, ¶6]	Neuroleptics, MAOIs, SNRIs, TCAs, anticonvulsants, antiparkinsonian drugs within 14 days prior to the screening visit and during the study.	Subjects who had diagnosed psychiatric or neurological disorders requiring treatment participated in the study if they were treated with medications other than those excluded and were on a controlled stable dose for at least 3 months prior to randomization.
Chronic DPN Pain [DOF, CSR 3015, p37, ¶1-2, ¶6]	Neuroleptics, MAOIs, SNRIs, TCAs, anticonvulsants, antiparkinsonian drugs within 14 days prior to the screening visit and during the study.	SSRIs were allowed if dosing was stable for at least 30 days prior to the screening visit. Subjects with diagnosed psychiatric or neurological disorders requiring treatment could participate in the study if they were treated with other medications than those excluded and were on a controlled, stable dose for at least 3 months prior to the screening visit.
One-Year Safety [DOF, CSR 3007, p32, ¶2, ¶4, ¶7]	Neuroleptics and MAOIs were prohibited within 14 days prior to the screening visit and during the study. If on a stable dose, TCAs were allowed. Any analgesics (including NSAIDs, COX-2 inhibitors, and opioids [including long-acting formulations and combination products]) other than the study drug and the allowed paracetamol medication were prohibited during the study.	TCAs were allowed if the subject was on a stable dose exclusively for pain but not for depression or other psychiatric disorders. SSRIs, SNRIs, benzodiazepines, mood stabilizers used as minor tranquilizers or hypnotics, antiparkinsonian drugs, and anticonvulsants were allowed if dosing was stable for at least 30 days prior to screening visit and would be kept approximately stable during study.

Use With Other Medications (cont)

"Can I prescribe both NUCYNTA® ER and tramadol for a patient?"

- Doctor, the Prescribing Information states that you should discontinue all other tapentadol and tramadol products in patients who are starting or currently receiving NUCYNTA® ER
- Patients should not take tramadol and NUCYNTA® ER simultaneously

"How is NUCYNTA® ER different from tramadol?"

- Doctor, there are many differences between NUCYNTA® ER and tramadol
- Let's focus on the following 3 differences: indication, mechanism of action, and regulatory status
- NUCYNTA® ER is indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
- Tramadol is indicated for the management of moderate to *moderately severe* pain[6] [ULTRAM PI, p2, col 1, ¶7]
- Although the clinical relevance is unclear, preclinical animal studies have shown that tapentadol is a mu-opioid agonist and a norepinephrine reuptake inhibitor
- Tramadol is a racemic mixture that appears to have 3 mechanisms of action: low mu-opioid agonism and weak inhibition of reuptake of both norepinephrine and serotonin[6] [ULTRAM PI, p1, col 1, ¶3, ¶5, ¶7]
- NUCYNTA® ER is a Schedule *II* controlled substance, whereas tramadol is generally not listed as a controlled substance, although there are a few states that have designated it a Schedule *IV* controlled substance
- Doctor, did this help to explain the important differences between NUCYNTA® ER and tramadol?

"Can NUCYNTA® ER and acetaminophen be given concomitantly?"

- Doctor, I'm sure you have some patients with chronic pain who would like to use both NUCYNTA® ER and acetaminophen in their treatment regimen
- Acetaminophen was permitted at certain points during clinical studies with NUCYNTA® ER.[1,2] According to the Prescribing Information for NUCYNTA® ER, acetaminophen was included in a set of interaction studies and there were no clinically significant findings.
- NUCYNTA® ER does not contain any acetaminophen in its formulation.
- [Ref 1: Buynak, p1788, col 2, ¶3] [Ref 2: Schwartz, p153, col 1, ¶1]

Use With Other Medications (cont)

Study	Acetaminophen Restrictions
Chronic Low Back Pain [DOF, CSR 3011, p40, bullets 5-7]	No acetaminophen was allowed during the washout period. During the titration period, acetaminophen was allowed as required as additional analgesic medication, limited to a TDD of 1000 mg. To enter the maintenance period, the subjects were not to use acetaminophen and had to be on a stable dose of study drug for the last 3 days of the titration period. During the maintenance period, the use of acetaminophen was prohibited; if absolutely necessary, intermittent use of up to 1000 mg for no more than 3 consecutive days for reasons other than the study-related chronic pain was permitted.
Chronic DPN Pain [DOF, CSR 3015, p38, bullet 1]	Paracetamol/acetaminophen treatment, up to 2000 mg daily, was allowed during the washout period as well as the open-label titration period (except during the last 4 days of titration) and was not allowed in the 3-day pain intensity evaluation period.
One-Year Safety [DOF, CSR 3007, p33, ¶2]	Paracetamol/acetaminophen 1000 mg daily as additional analgesic medication was allowed for a maximum of 7 consecutive days and no more than 14 days out of 30 days during the study.

Use in Specific Populations

"What are the guidelines and/or criteria used to differentiate between moderate and severe hepatic impairment?"

- In clinical studies with NUCYNTA® ER, patients were excluded if they had moderate to severe hepatic impairment, or AST or ALT greater than 3 times the upper limit of normal.[1,2,5]
- A study with the immediate-release formulation of tapentadol in subjects with hepatic impairment showed higher serum concentrations of tapentadol than in those with normal hepatic function; therefore, tapentadol should be used with caution in patients with moderate hepatic impairment.
- According to section 2.4 of the NUCYNTA® ER Prescribing Information, patients with moderate hepatic impairment should be initiated using 50 mg of NUCYNTA® ER and administered no more than once every 24 hours.
- The maximum recommended dose for patients with moderate hepatic impairment is 100 mg of NUCYNTA® ER once daily.
- NUCYNTA® ER has not been studied in patients with severe hepatic impairment, therefore, use of NUCYNTA® ER in this population is not recommended.
- [Ref 1: Buynak, p1788, col 2, ¶3] [Ref 2: Schwartz, p152, col 1, ¶5; col 2, ¶1] [Ref 5: DOF, CSR 3011, p34, bullet 11] [Ref 5: DOF, CSR 3015, p31, bullet 9]

Pharmacokinetics

"Does NUCYNTA® ER last 12 hours? Is it true twice-daily (bid) dosing?"

- According to the Prescribing Information, NUCYNTA® ER should be dosed twice daily.
- NUCYNTA® ER was FDA approved based on clinical trials that demonstrated efficacy using 100 mg to 250 mg twice daily.[1,2]
- [Ref 1: Buynak, p1789, col 1, ¶1; p1791, col 2, ¶3] [Ref 2: Schwartz, p152, col 2, ¶5; p156, col 1, ¶1; col 2, Fig 2; p157, col 1, ¶1]

"It is not uncommon to dose Oxycontin® TID. Is it anticipated that NUCYNTA® ER will trend toward TID dosing as well?"

- Doctor, I am glad to hear that you are considering the administration of NUCYNTA® ER to that of Oxycontin®.
- According to the prescribing information, NUCYNTA® ER should be dosed twice daily. NUCYNTA® ER was FDA approved based on clinical trials that demonstrated efficacy using 100-250mg twice daily[1,2,8]. [Citations: NUCYNTA® ER PI Section 2 and 14, Buynak et al, 1789, col1 , Schwartz et al, 153, col1]
- Do you have a specific patient in mind that you are considering switching from Oxycontin® to NUCYNTA® ER?

"Where is the major absorption taking place in the body for NUCYNTA® ER? Are the blood levels dependent on a fully functioning bowel?"

- The exact site(s) of where tapentadol is absorbed in the gastrointestinal (GI) tract following oral administration is unknown. Pharmacokinetic studies were not designed to elucidate information on site of absorption nor the absorption profile in subjects with abnormal bowel function.
- According to Phase III clinical efficacy study protocols, patients with significant GI disorders that in the investigator's opinion could affect efficacy or safety assessments were excluded from the trials[1,2,5]. [DOF, CSR 3011, p34, DOF, CSR 3015, p31, Buynak 2010, p1788, col2, Schwartz 2010,152,col1-2] The decision to exclude patients was left to the discretion of the investigator.

Access & Affordability

"How much does NUCYNTA® ER cost? Is it covered on X plan?"

- I realize that cost is a valid concern with a new medication
- Let me assure you that our cost savings program will help make NUCYNTA® ER affordable for chronic pain patients
- By using the NUCYNTA® ER Pay No More Than (PNMT) $25 Savings Card, patients with commercial health insurance will pay *no more than $25* for their monthly prescription co-pay of NUCYNTA® ER
- The NUCYNTA® ER PNMT $25 Savings Card is valid for up to 14 prescriptions (not to exceed 12 uses at the same dose) with a maximum benefit of $100 per fill
- The PNMT $25 Savings Card is easy for patients to use and makes the monthly cost of NUCYNTA® ER affordable, putting it on par with medications that have Tier 2 health plan status
- Let me provide you with a supply of NUCYNTA® ER PNMT $25 Savings Cards. I encourage you to provide one to every patient who receives a NUCYNTA® ER prescription
- Also, be sure to visit our Web site at www.NUCYNTA.com to learn more about the benefits of NUCYNTA® ER

"Is there a way to make NUCYNTA® ER more affordable for my patients?"

- Yes. With the NUCYNTA® ER Pay No More Than $25 Savings Card, patients with commercial health insurance will *pay no more than $25* for their monthly prescription co-pay of NUCYNTA® ER.
- The savings card is valid for up to 14 prescriptions (not to exceed 12 uses at the same dose) with a maximum benefit of $100 per fill.
- The NUCYNTA® ER Pay No More Than $25 Savings Card is easy for patients to use and makes the monthly cost of NUCYNTA® ER affordable, putting it on par with medications that have Tier 2 health plan status.
- NUCYNTA® ER Pay No More Than $25 Savings Cards are available at www.nucynta.com
- Additional patient assistance programs for NUCYNTA® ER can be found at www.access2wellness.com.

Access & Affordability (cont)

"Is NUCYNTA® ER available via the patient assistance program?"

- Yes, NUCYNTA® ER is available via the patient assistance program. Patients/providers should call 1-800-652-6227 to request an application.

The application is also available at Access2wellness.com.
((THE FOLLOWING IS "FPO"))

01MC334	Access 2 Wellness Patient Slim Jim with TELL A FRIEND brochure
01MC337	Access 2 Wellness Two-Sided Poster
01MC375	Access 2 Wellness Patient Slim Jim with TELL A FRIEND brochure (in Spanish)
01MC376	Access 2 Wellness Slim Jim Holder (in Spanish)

"How do I submit for the pharmacy stocking rebate?" (Independent pharmacist)

- I would be happy to provide you with the information needed to submit for the pharmacy stocking rebate.
- Let me remind you that we offer a retail stocking rebate of up to 15% total rebate for retail stocking during the 30-day promotion period (promotion ends September 30, 2011) MAXIMUM 2 BOTLES OF EACH STRENGTH
- All offers contingent upon purchase by September 30, 2011
- Payment will be made by check
- A complete listing, including
  - Name and address of each retail pharmacy
  - Number of bottles
  - Date stocked
- Must be sent no later than November 15, 2011 to:
- Melanie Berstler at MBerstler@its.jnj.com at Janssen Pharmaceuticals, Inc.

Standard MIR Response

"Is there information about [off-label topic]?"

- While I'm unable to address that specific question, I want to let you know that Janssen is committed to providing you with the information that you request and will follow up with you as soon as possible
- Discussions about [off-label topic] are not within FDA-approved labeling and, therefore, I can't respond
- However, I can quickly submit an electronic Medical Information Request to our Customer Communication Center, and they can provide you with additional information
- Let me fill out an electronic form and get your signature, and the Customer Communication Center will assist you

References

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3. Vanderah TW. Pathophysiology of pain. *Med Clin North Am*. 2007;91(1):1-12.

4. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol*. 2008;16(5):405-416.

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8. NUCYNTA® ER (tapentadol) extended-release oral tablets [package insert]. Titusville,NJ: Janssen Pharmaceuticals, Inc; August 2011.